CTCAE v3.0: Development of a Comprehensive Grading System for the Adverse Effects of Cancer Treatment

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Multiple systems have been developed for grading the adverse effects (AEs) of cancer treatment. The National Cancer Institute Common Toxicity Criteria (CTC) system has substantially evolved since its inception in 1983. The most recent version, CTCAE v3.0 (Common Terminology Criteria for Adverse Events version 3.0) represents the first comprehensive, multimodality grading system for reporting the acute and late effects of cancer treatment. The new CTC requires changes in the application of AE criteria including new guidelines regarding late effects, surgical and pediatric effects, multimodality issues, and for reporting the duration of an effect. It builds on the strengths of previous systems, represents a considerable effort among hundreds of participants, and signifies an international collaboration and consensus of the oncology research community. This article updates recent progress in the evolution of adverse effects grading systems and reviews the development of CTCAE v3.0.

The recognition and reporting of the adverse effects (AEs) of cancer treatment have long been essential activities in the conduct of clinical trials.[1] More than 500 distinct kinds of AEs have been associated with modern cancer therapy. They range in severity from minor, asymptomatic changes noted on physical examination to life-threatening injuries or death. The National Cancer Institute (NCI) Common Toxicity Criteria system (CTC v1.0) was first created in 1983 to aid in the recognition and grading adverse effects of chemotherapy. It was updated and expanded in 1998 (CTC v2.0) but remained focused on acute effects.[2] In an effort to create a single grading platform incorporating full surgical, late effects, and pediatric criteria, the NCI has guided the development of a significant revision of the CTC (Common Terminology Criteria for Adverse Events version 3.0 [CTCAE v3.0]). The third version of the CTC has been renamed the Common Terminology Criteria for Adverse Events v3.0. This article updates recent progress in the evolution of adverse effects grading systems and reviews the development of CTCAE v3.0, especially as it relates to a recent toxicity criteria and reporting workshop (Late Effects of Normal Tissues [LENT IV]).

The term adverse event indicates any new finding or undesirable event that may or may not be attributed to treatment. Some AEs are clinical changes or health problems unrelated to the cancer diagnosis or its treatment. Definitive assignment of attribution cannot always be rendered at the time of grading. In this article, we also use the common vernacular term "adverse effect," which indicates an event is thought to be related to treatment.

Evolution of the CTC

The evolution of various AE grading systems and the history of their modality origins have been reviewed elsewhere.[3] Table 1 summarizes the

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Table 1. The Evolution of Toxicity Grading Systems(1979-1998)

System	*No. of Criteria*	*No. of Organs*	*Modality*	*Phase*
WHO (1979)	28	9	Chemo	Acute
CTC (1983)	18	13	Chemo	Acute
RTOG/EORTC-Acute (1984)	14	13	RT Acute	Acute
RTOG/EORTC-Late (1984)	16	13	RT Late	Late
LENT (1995)	152	22	RT Late	Late
CTC v 2.0 (1998)	260	22	All*	Acute

Abbreviation: WHO, World Health Organization.
*Limited pediatric and surgical criteria.

most widely used systems over the last 20 years. In 1998, the NCI released a revised and markedly expanded version of the CTC (CTC v2.0) designed to update the original CTC. Among the changes was greater specificity in criteria language and the systematic inclusion of criteria for grading the acute effects of radiotherapy. This revision did not include criteria for the late effects of treatment. The NCI continued to rely on the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) Late Morbidity System created in 1984 that was appended to the CTC.[4] In addition, CTC v2.0 contained only limited criteria applicable to surgery and pediatric issues.

CTC v2.0 was implemented in March 1998 and has been widely adopted by numerous cooperative and industry groups. The broad acceptance and extensive use of the CTC v2.0 grading system has also highlighted the need to improve the reporting of AEs in the area of surgical effects, late effects, and pediatrics.

The NCI Cancer Therapy Evaluation Program (CTEP) has been the administrator of the CTC system since its inception. To oversee its further development and implementation, CTEP leadership created the CTC Development Team in 2001. The Development Team was led by A. Dimitrios Colevas, Senior CTEP Investigator, and composed of representatives of relevant NCI Branches and investigative groups.

In gathering feedback from investigators, the CTC Development Team received input from 3 advisory panels: the Surgical Effects Panel, the Late Effects Workshop CTC Committee, and the Pediatric Panel. This article discusses the development process and the meeting conducted by the Late Effects Workshop CTC Committee.

Late Effects Workshop

The shortcomings of the RTOG/EORTC Late Effects System were apparent by the early 1990s, prompting the development of the Late Effects of Normal Tissue (LENT-SOMA) scales in 1995.[5] Since then, the LENT-SOMA system has been evaluated by a number of institutions and found to more comprehensively capture late effects.[6] However, comparison of LENT-SOMA to the RTOG/EORTC and CTC systems has shown inconsistent concordance and correlations, indicating the need for a common system.[7] In addition, the cooperative groups and investigators have found the use of multiple systems has created difficulties in their routine clinical trials applications and in comparing results between studies and institutions.

Noting the rapid adoption and success of CTC v2.0, RTOG leaders initiated an effort to amend the CTC with a more complete set of late effects criteria. Because a large number of issues and criteria were at stake, a workshop forum was selected for further criteria development. The Late Effect Workshop (LENT IV) was held in April 2002 in St. Petersburg, FL.[8] As the fourth in a series of meetings dedicated to the assessment and reporting of late effects, the meeting was initially designed to revise the LENT-SOMA criteria for inclusion into the planned CTC revision. However, with strong support from the NCI and the pharmaceutical industry, the workshop was enlarged to include a wide variety of multidisciplinary experts, including surgeons, medical oncologists, clinical research associates, biologists, statisticians, and other specialists. Twelve representatives from the EORTC, 8 representatives from the CTEP Surgical Effects Panel (as well as other surgeons), and 3 representatives from the

Table 2. Late Effects Workshop CTC Committee

CNS
Bill Regine (R/O) (Chair), Joanne Ley (CRA), Paul Sperduto (R/O), Jay Loeffler (R/O) Andrew Sloan (SEP-Neurosurg), René Mirimanoff* (EORTC R/O), Tom Merchant (R/O-Peds), Lisa DeAngelis (Neuro Oncology)
Head & Neck
David Rosenthal (R/O) (Chair), Jackie Fisher (CRA), Adam Garden(R/O), David Brizel (R/O), Volker Budach (R/O) (EORTC), Drew Ridge (SEC H&N Surg), Barbara Murphy (Med Onc), Stan Dische (R/O), Michelle Saunders (R/O), Avi Eisbruch (R/O), Nelson Rhodus (Oral Med)
EYE
Adam Garden (R/O) (Chair), Rolf-Peter Mueller* (EORTC R/O), Tim Murray (SEC-Opthal), Stella Kim (Opthal), Lisa Chin (CRA)
HEME
Charles Scarantino (R/O) (Chair), Wilson Mertens (Med Onc)
Lung
Roger Byhardt (R/O) (Chair) Mitchell Machtay (R/O), Larry Marks (R/O), Mitchell Anscher (R/O), Bill Small R/O), Ken Rosenzweig (R/O), Michelle Saunders (R/O), Frank Detterbach (SEC-Thorac Surg), Suresh Senan (EORTC R/O), Corey Langer (Med Onc), Jean Stern (CRA)
Heart
Sandy Constine (Chair), Jean Stern (CRA), Steven Lipshultz (Cardiol), Cindy Schwartz (Ped Onc), Veronique Coen (EORTC R/O), Michelle Saunders (R/O)
GI
Ross Abrams (R/O) (Chair), Lisa Chin (CRA), Neil McGinn (R/O), Larry Kleinberg (R/O), Chris Willet (R/O) David Jaques (SEC GI), Francois Bosset* (EORTC R/O)
Breast
Marie Taylor (R/O) (Chair), Beryl McCormick R/O), Harry D. Bear (SEC Breast Surg), Geertjan van Tienhoven (R/O)(EORTC)
Skin
Stan Dische (Chair)(R/O), Michelle Saunders (R/O), Todd Wasserman (R/O), Jackie Fisher (CRA)
GU
Sandler (R/O)(Chair), Bonnie Sauder (CRA), Michel Bolla (R/O)*(EORTC), Julie Kish (M/O), Mack Roach (R/O), Adam Dicker (R/O), John Wei (Urol), John Seigne (Urol), Sirinisian "Vijay" Vijayakumar (R/O), Mark Sobzcak (R/O), Clement Gwede (RN, PhD)
GYN
Kathryn Grevens (R/O) (Chair), Deborah Watkins-Bruner (RN PhD), Whitney (GYN/ONC-SEC GOG) Anuja Jhingran (R/O), Beth Erickson (R/O), Brigid Miller (GYN/ONC), Isabelle Barillot* (R/O) (EORTC), Joanne Ley (CRA)
Musculoskeletal
Delaney (Chair) (R/O), Bill Kraybill (Surg), Sandy Constine (R/O), Ronald Keus* (R/O)(EORTC) Brian O'Sullivan (R/O), Aileen Davis (Clinical Scientist), Bonnie Sauder (CRA) Mark C. Gebhardt (Surg), Lynn Gerber (Rehab Medicine)

Abbreviations: R/O, radiation oncologist; SEC-surgeon, Surgical Effects Committee for CTEP; CRA, clinical research asociate.

Childrens Oncology Group participated in criteria development.

The aims of the workshop included the completion of surgical effects criteria begun by the CTEP Surgical Effects Panel, creation of new guidelines for the temporal classification of AEs, exploration of the role of informatics, and presentation of state of the science reviews on toxicity metrics. Multiple reports from this workshop are included elsewhere in this issue. The conference was endorsed by a number of organizations, including the RTOG, the EORTC, the American College of Surgeons Oncology Group (ACOSOG), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the American Society of Therapeutic Radiology and Oncology (ASTRO). Table 2 lists the site subcommittees and participants of the Late Effects Workshop CTC Committee.

Workshop participants spent a full day in round table sessions, revising and creating new CTC criteria. In addition to CTC v2.0, a number

of other existing grading systems were used as resources including the LENT-SOMA system, the DISCHE grading dictionary,[9] and the RTOG/EORTC Late Morbidity System.

General guidelines for the construction of CTC grading criteria were reviewed. Grade 1 effects are minimal and usually asymptomatic and do not interfere with functional endpoints. Interventions or medications are generally not indicated for these minor effects. Grade 2 effects are considered moderate, are usually symptomatic, and interventions such as local treatment or medications may be indicated. They may or may not interfere with specific functions but not enough to impair activities of daily living.

Grade 3 effects are considered severe and very undesirable. There are usually multiple, disruptive symptoms. More serious interventions, including surgery or hospitalization, may be indicated. Grade 4 effects are potentially life threatening, catastrophic, disabling, or result in loss of organ, organ function, or limb.

In developing criteria, the workshop participants were asked to pay close attention to the critical threshold in severity scaling when moving from a grade 2 to a grade 3. Low-grade events (grades 1 and 2) are considered tolerable and manageable and should be clearly distinguished from severe or very undesirable high grade events (grades 3 and 4).

At the end of the workshop, more than 300 new criteria were created. The new criteria were collated and forwarded to the NCI-CTC Development Team for review.

New Principles of CTCAE v3.0

A number of *new principles* were established at the workshop regarding the need for fundamental changes in the methods of grading and reporting adverse effects.

Late effects and acute effects criteria will be merged into a single uniform system and applied without a predetermined time-based designation. In an era of complex multimodality integration, the designation of acute versus late effects (or subacute, consequential, and so on) will be a determination made by the investigator(s) upon reviewing and interpreting aggregate data from a clinical trial. The previously used "90-day rule" for determining whether an AE is an acute or late effect will no longer be arbitrarily applied because each study is unique. Investigators are encouraged to report all observations by using individual CTC criteria that best describe the injury (a description-driven approach). The clinical descriptions of AEs in the new CTC will remain largely recognizable as classical acute and late reactions (eg, mucositis, fibrosis), but this should not interfere with identifying new temporal patterns of injury.

The new CTC system is designed to be applied to all modalities. When possible, grading criteria should not be modality specific. Many AEs are modality nonspecific (eg, dysphagia) or may be the result of multiple modalities (eg, diarrhea). Applying the same criteria, regardless of causative agent, promotes uniformity in grading and helps to avoid the notion of attributing "blame" to any particular modality when in many cases tissue injury is multifactorial. As noted earlier, a description-driven approach should be used in the application of the CTC criteria. Investigators and research personnel should apply the most appropriate CTC language that best describes the event. However, there are some exceptions in the CTC that are modality specific (eg, surgery/intraoperative injury).

The duration (or the chronicity) of an AE should be determined by longitudinal serial evaluations as defined in each protocol document. In general, duration is not an intrinsic part of the grading criteria for a given effect. This approach is somewhat analogous to the use of survival or local-regional control methodology to evaluate change in an endpoint over time. However, it is also recognized that the grade of an AE may change over time or that an AE may spontaneously resolve, be corrected by intervention, or reappear at a later time. There are currently no widely accepted reporting standards for characterizing the duration of an AE (an area for further investigation).

The unexpected serious and life-threatening (grades 3-4) consequences of surgery are the focus of immediate surgical reporting. In general, it is not useful to capture all of the acute and expected events associated with surgery in the immediate postoperative period. These should not be collected as a routine assessment in NCI-sponsored trials, but selected elements may be collected depending on the nature of the trial. These events should be as a consequence of the surgery but not the surgery itself. For example, hospitalization for colectomy itself is not an adverse event, but reoperation for

Table 3. The Evolution of the NCI Common Adverse Effects Grading System

System	*No. of Criteria*	*No. of Organs*	*Modality*	*Phase*
CTC (1983)	18	13	Chemo	Acute
CTC v2.0 (1998)	260	22	All*	Acute
CTCAE v3.0 (2003)	370	All	All	Acute and late

*Limited pediatric and surgical criteria.

anastomotic leak, however, would be a gradable and reportable adverse event. The lasting or late effects of surgery can also be collected according the protocol-specific directions.

The purpose of the CTC is to provide a "grading dictionary" to help recognize and rank the severity of effects. It is not designed to summarize the global level of toxicity produced by any particular treatment program. A large number of individual AEs are recorded on any given trial. The resulting data then require substantial interpretation to best characterize the overall toxicity profile of a treatment program. This may be done by grouping AEs in various ways (eg, hematologic versus nonhematologic) and reporting the percent of the group that exhibited high- versus low-grade events. Methods to summarize toxicity are still not well defined, and further work in this area is needed.

CTC criteria cannot themselves determine an acceptable toxicity profile. There are no standards at this time for what constitutes a high, low, or acceptable toxicity profile. There are no broad guidelines for when a particular level of risk or AE profile for a given regimen becomes "unacceptable." Evaluating the therapeutic ratio is a judgment that must be determined on a trial-by-trial and patient-by-patient basis by the investigators or physicians involved. Similarly, comparison of toxicity profiles between various treatment approaches should be done with extreme caution because cancer outcomes and patient heterogeneity may also significantly differ.

CTCAE v3.0

The third version of the CTC has been renamed as Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). The purpose of renaming is to move away from the term toxicity, which implies causation and does not fit the jargon commonly used across all modalities. It is scheduled for full distribution to NCI-sponsored organizations in the Spring of 2003 and will be available on the CTEP web site (http://ctep.info.nih.gov/CTC3/ctc/htm).[10] It is anticipated that after October 2003 all NCI-sponsored trials will use CTCAE v3.0. CTC v2.0, and the RTOG/EORTC Late Radiation Morbidity Scoring System will continue to be supported for legacy trials launched before the availability of version 3.0.

CTCAE v3.0 (like CTC v2.0) is generally organized by organ system categories. A few new categories were added including cardiac arrhythmia, cardiovascular, cardiac/general, growth and development, and death. CTCAE v3.0 contains approximately 570 criteria, up from 250 in CTC v2.0 (Table 3). About 35 criteria contain list of values for specifying anatomic sites (eg, fistula–rectal, esophageal, tracheal, and so on) or other subclassifications, resulting in about 900 site-specific AE criteria for grading (with subclassifications included).

Summary

CTCAE v3.0 represents the first comprehensive, multimodality grading system to include both acute and late effects. We believe that it will greatly facilitate the standardized reporting of AEs, comparison of outcomes between trials and institutions, and promote a more complete recognition and reporting of adverse effects. This document has evolved over 20 years of use and has substantially matured in recent years to become a vital multimodality clinical trials tool. The development of CTCAE v3.0 has been an enormous effort among hundreds of participants and represents an international collaboration and consensus of the oncology research community.

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